

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 November 2003 (27.11.2003)

PCT

(10) International Publication Number
WO 03/097039 A1

(51) International Patent Classification⁷: **A61K 31/40**,
47/02, 9/20

(21) International Application Number: PCT/CA03/00710

(22) International Filing Date: 15 May 2003 (15.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2,385,529 21 May 2002 (21.05.2002) CA

DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant and

(72) Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50
Old Colony Road, Toronto, Ontario M2L 2K1 (CA).

Published:

— with international search report

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CH, CN, CO, CR, CU, CZ,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABLE DOSAGE FORMS COMPRISING ATORVASTATIN CALCIUM

(57) Abstract: Solid compositions for oral administration comprising atorvastatin calcium and a sodium or potassium compound, for which an aqueous dispersion is capable of producing a pH above 11.

USPN: 10/828,398
DOCKET NO: PC 25826A
FILED: APRIL 20, 2004

WO 03/097039 A1

STABLE DOSAGE FORMS COMPRISING ATORVASTATIN CALCIUMFIELD OF INVENTION

5

This invention relates to solid pharmaceutical compositions for oral administration comprising atorvastatin calcium, and improvement of the stability of such compositions.

10 BACKGROUND OF THE INVENTION

Atorvastatin is a synthetic lipid-lowering agent, and is disclosed and claimed in U.S. patent 5273995.

15 Tablets comprising atorvastatin as the hemi-calcium salt (known as atorvastatin calcium) are sold in the United States as elsewhere under the tradename Lipitor™.

Atorvastatin is a member of a class of compounds known as "statins". These
20 compounds are HMG-CoA reductase inhibitors, and are used as antihypercholesterolemic agents.

Some of these compounds and, in particular, fluvastatin, pravastatin and atorvastatin, have in their molecule a non-esterified hydroxy acid moiety, and
25 thus will form basic salts, such as sodium or calcium salts. When these compounds are in the acid form, they are relatively unstable and are prone to degradation into the corresponding lactones.

It is known from the prior art that stable compositions comprising such
30 compounds can be made either by using these compounds in the form of basic salts, or alternatively, if the acid form is used, including in the composition a basic excipient so as to keep the compound in a basic environment.

™ - Registered trademark.

There are several such prior art publications that deal with stabilization of statins having a non-esterified hydroxy acid moiety.

- 5 U.S. patent 5180589 deals specifically with pravastatin. The disclosure explains that stability of pravastatin in a composition may be improved by including a basifying agent to raise the pH of an aqueous dispersion of the composition to at least 9 and preferably at least 9.5. Nine examples are given along with data which confirms that, in each example, inclusion of magnesium
10 oxide as basifying agent inhibits conversion of the pravastatin to the lactone. The disclosure deals only with pravastatin in its acid form, and not with basic salts of pravastatin such as pravastatin sodium. Pravastatin sodium already being basic, does not require inclusion of a basifying agent in the tablet to improve stability, so long as the tablet contains no acidic excipient (inactive
15 ingredient). This publication makes no mention of atorvastatin calcium.

- Similarly, U.S. patent 5356896 relates to stabilization of solid compositions of fluvastatin against lactone formation by inclusion of a basifying agent so that an aqueous dispersion of the composition will have a pH of at least 8. The
20 disclosure and claims of this patent appear to confuse fluvastatin with its basic salts, and in particular appear to confuse fluvastatin with fluvastatin sodium. All of the examples in the disclosure show compositions which contain, as the active drug, fluvastatin and not fluvastatin sodium, and the examples confirm that compositions which comprise fluvastatin along with a basifying agent are
25 stable. However, all of the claims of this patent are limited to compositions which comprise the drug in the form of a basic salt and not the acid form. Moreover, when the active ingredient is fluvastatin sodium, and not fluvastatin, compositions are stable without the inclusion of a basifying agent, so long as the compositions do not include an acidic excipient. A basifying
30 agent is thus not needed for stability in the case of fluvastatin sodium. It thus appears that the claims erroneously state the drug to be in the form of basic salt, whereas the invention, if any, relates to the drug in the form of the

hydroxy acid. Again, this publication makes no reference to atorvastatin calcium.

- 5 WO 00/35425 discloses compositions comprising an active substance that is a HMG-CoA reductase inhibitor, wherein that active substance is one which is capable of providing a pH in the range of 7 to 11. The term "active substance" is defined as meaning the HMG-CoA reductase inhibitor alone or a mixture thereof with a small amount of a buffering agent. The essence of the
10 invention is that, by using an active substance which provides a pH in the range of 7 to 11, it is possible to achieve improved stability even if the final composition in which it is contained exhibits pH below 9. In other words, by creating an environment locally within each particle of the active substance such that a dispersion of such particles in water would have a pH of 7 to 11, it
15 is not necessary that the entire mass of the composition be highly basic.

- WO 00/35425 has only six examples. The first five all comprise pravastatin sodium as the active drug and the sixth comprises atorvastatin calcium along with dibasic sodium phosphate as buffering agent. The concluding paragraph
20 of the disclosure states that the compositions of all six examples provide excellent stability, with essentially no degradation of the pravastatin or atorvastatin observed. However, as aforesaid, pravastatin sodium is a basic salt and does not require further stabilization in the absence of an acid, so that it is not surprising that the composition of examples 1 to 5 are stable.
25 Moreover, with respect to example 6, as will be explained hereafter, while atorvastatin calcium is stable against conversion to the lactone in the absence of an acid, it is prone to other types of degradation, and in particular oxidation, even at pH of 7 to 11. It is thus more difficult to provide stable compositions for atorvastatin calcium than for pravastatin sodium or fluvastatin sodium. It
30 thus appears that the statement in WO 00/35425 that the composition of example 6 is stable is likely erroneous. It may be that not all degradation products were measured, but only the lactone.

- U.S. patent application 2002/0035142 discloses stabilized compositions
35 comprising a statin that is a hydroxy acid or salt thereof and a stabilizing

amount of an amido-group containing polymer or an amino-group containing polymer. The compositions are said to provide stability against lactone formation. However, where the active ingredient is atorvastatin calcium, such compositions will not provide good stability against types of degradation other
5 than lactone formation.

As aforesaid, atorvastatin calcium is disclosed in U.S. patent 5273995. The processes of this patent produce atorvastatin calcium in amorphous form. Because atorvastatin calcium is a basic salt of atorvastatin, like pravastatin
10 sodium and fluvastatin sodium, it is not unstable against formation of the lactone unless mixed with other acidic compounds. However, it is more prone than pravastatin sodium and fluvastatin sodium to other types of degradation, including oxidation, even as the calcium salt.

15 U.S. patent No. 5969156 teaches new crystalline forms of atorvastatin calcium which are designated as Form I, Form II, Form IV, and are said to be more stable than the amorphous form. Lipitor™ tablets comprise atorvastatin sodium in crystalline Form I.

20 U.S. patent 6126971 relates specifically to stable solid dosage forms comprising atorvastatin calcium. The disclosure confirms that this compound is unstable in that it is susceptible to heat, moisture, low pH environment and light; and that in an acid environment, in particular, the hydroxy acid will degrade to lactone. Since the calcium salt is basic and not acidic,
25 compositions comprising atorvastatin calcium do not require stabilizing against formation of the lactone, so long as the composition does not comprise an acidic excipient. However, as aforesaid, atorvastatin calcium is still unstable to other types of degradation even in the absence of an acid.

30 U.S. patent 6126971 teaches that compositions comprising atorvastatin calcium, even in the absence of an acidic excipient, will exhibit improved stability if the composition comprises at least one excipient that is also a salt of an alkaline earth metal such as calcium or magnesium. All of the examples
35 in this patent comprise atorvastatin calcium as the active ingredient, and

calcium carbonate as the stabilizer. The test data in the disclosure confirms that tablets comprising calcium carbonate are more stable than tablets without calcium carbonate.

- 5 U.S. patent 6126971 thus teaches that, when atorvastatin is in the form of the calcium salt (calcium being an alkaline earth metal), and even in the absence of an acidic ingredient, stability is improved by inclusion of an excipient that is another salt of an alkaline earth metal. This patent thus leads the reader to conclude that, for atorvastatin calcium formulations, metal salts other than
10 those of alkaline earth metals are either ineffective as stabilizers or are less effective as stabilizers than alkaline earth metal salts.

The disclosure of U.S. patent 6126971, does not specify whether the atorvastatin calcium being in the examples used is the amorphous form or
15 one of the crystalline forms disclosed in U.S. patent 5969156. However, as Lipitor™ tablets contain crystalline Form I, which is the most stable form, it appears that the atorvastatin calcium used in the examples is crystalline Form I.

- 20 It has been found when the atorvastatin calcium is in amorphous form, the compositions within the scope of U.S. patent 6126971 do not enable good stability. Moreover, even Lipitor™ tablets exhibit slow degradation of the atorvastatin calcium content.

- 25 In view of this prior art, one objective of the present invention is to enable solid compositions for oral administration comprising atorvastatin calcium that are stable, even when the atorvastatin calcium is an amorphous form. Another objective of the invention is to enable atorvastatin calcium tablets that
30 are stable without comprising an excipient that is an alkaline earth metal salt. Another objective of the invention is to enable atorvastatin calcium tablets that are more stable than Lipitor™ tablets.

DESCRIPTION OF THE INVENTION

As aforesaid, WO 00/35425 teaches that atorvastatin sodium is best stabilized by incorporating it into particles for which the pH of an aqueous dispersion is
5 between 7 and 11; and U.S. patent 6126971 teaches that atorvastatin calcium is best stabilized by including in the composition an excipient that is also an alkaline earth metal salt (as is atorvastatin calcium itself).

In light of this prior art, it has now been surprisingly found that atorvastatin
10 calcium is best stabilized against degradation, including oxidation, by incorporating a basic sodium or potassium compound along with the atorvastatin calcium in the composition, or in particles within the composition, such that an aqueous dispersion of the composition or of the particles is capable of providing a pH above 11.

15

Accordingly, compositions within the scope of the present invention will comprise atorvastatin calcium and at least one sodium or potassium compound, such that either:

- 20 i) an aqueous dispersion of the composition is capable of producing a pH of above 11; or

- ii) the composition comprises particles which further comprise said atorvastatin calcium and said sodium or potassium compound, and an aqueous dispersion of said particles is capable of producing a pH of above 11.

The sodium or potassium compound may be a hydroxide or a salt of a weak acid. Suitable compounds will include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, tribasic sodium phosphate, and tribasic potassium phosphate. The sodium or potassium compound may be either anhydrous or hydrated.

Especially preferred are tribasic sodium phosphate and tribasic potassium phosphate. Most preferred is tribasic sodium phosphate.

The composition will preferably be tablets.

The composition will also preferably include one or more excipients other than the sodium or potassium compound.

Such excipients may include, for example, any or all of:

- i) A binder, such as microcrystalline cellulose.
- ii) A disintegrant, such as starch, croscarmellose sodium, sodium starch glycolate, or crospovidone.
- iii) A lubricant, such as magnesium stearate.
- iv) A glidant, such as colloidal silicon dioxide.

When the composition is in the form of tablets, the tablets may be made by a direct compression process, wherein the ingredients are mixed together in dry form and the mixture is directly compressed into tablets.

5

If the powder mixture does not flow well enough for direct compression, then the flow may be improved by either a wet granulation or a dry granulation process.

- 10 In a wet granulation process, ingredients are made into a wet mass using water or an organic solvent, in which a binder may optionally be dissolved, and the wet mass is then dried and milled into free-flowing granules. Alternatively, flow may be improved by a dry granulation process, also known as compaction or slugging, in which a mixture of ingredients is first
- 15 compressed into compacted material, which is then milled into granules, which are then recompressed into the final tablets.

The invention will be better understood from the following examples which are meant to be illustrative and not limiting the scope of the invention.

20

EXAMPLES

Examples 1 to 4 were made as follows:

Example No.:	1	2	3	4
25 Atorvastatin Calcium Amorphous	5.4	5.4	5.4	5.4
30 Sodium Carbonate Monohydrate	124.6	0	0	0
Sodium Citrate Dihydrate	0	124.6	0	0
35 Sodium Phosphate Dibasic Anhydrous	0	0	124.6	0
Sodium Phosphate Tribasic, Anhydrous	0	0	0	124.6
40	130.	130.	130.	130.

For each of the four examples, the ingredients were mixed in the proportion shown. The mixture was then compressed into slugs using a tablet press. The slugs were then ground up into granules, which are particles comprising atorvastatin calcium and the sodium compound. The granules were
5 recompressed into tablets at a weight of 130 mg each. Each tablet thus contained about 5.4 mg of atorvastatin calcium, which is equivalent to about 5 mg of atorvastatin, allowing for a water content of about 4 percent.

Sample tablets of each of the four examples and also sample tablets of
10 Lipitor™ were then stored at 60°C for two weeks. Samples of each, along with samples that had been kept at room temperature, were then tested for degradation products by a High Performance Liquid Chromatographic (HPLC) method. The amounts by which the total degradation products in the samples stored at 60°C exceeded the total degradation products in the samples stored
15 at room temperature were as follows:

	<u>Example #</u>	<u>Stabilizer</u>	<u>Increase in Degradation Products at 60°C Levels</u>
20	1	Sodium carbonate Monohydrate	1.16%
	2	Sodium citrate Dihydrate	1.27%
	3	Sodium phosphate dibasic Anhydrous	1.52%
	4	Tribasic sodium phosphate Anhydrous	0
	Lipitor™	Calcium carbonate	0.18%

25

For the tablets of examples 1 and 4, the pH of an aqueous dispersion (and also the pH of an aqueous dispersion of the granules from which they were made) exceeds 11; whereas for examples 2 and 3 the pH is less than 11. Examples 1 and 4 are thus examples of the present invention; examples 2
30 and 3 are not examples of the present invention, but are included for comparison purposes.

It can be seen that the stability of the tablets of examples 1 and 4 is superior
35 to that of examples 2 and 3. Also, and very surprisingly, the stabilizing effect of tribasic sodium phosphate in example 4 is even better than that of sodium carbonate, in example 1, despite the fact that the pH of the aqueous

10

dispersions for both exceed 11. Use of tribasic sodium phosphate in compositions of the present invention thus enables stability even better than that of Lipitor™.

- 5 As tribasic potassium phosphate is very similar to tribasic sodium phosphate in physico-chemical characteristics, it may be concluded that tribasic sodium phosphate and tribasic potassium phosphate are both especially preferred as stabilizers for atorvastatin calcium, in compositions of the present invention.

10

15

20

25

CLAIMS

1. A solid composition for oral administration comprising atorvastatin
5 calcium and at least one sodium or potassium compound, such that
either an aqueous dispersion of the composition is capable of providing
a pH above 11, or alternatively the composition comprises particles
which comprise said atorvastatin calcium and said sodium or
potassium compound, and an aqueous dispersion of said particles is
10 capable of producing a pH above 11.
2. A composition of claim 1 wherein the atorvastatin calcium is
amorphous.
- 15 3. A composition of claim 1 or 2 that is a tablet.
4. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is sodium hydroxide.
- 20 5. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is potassium hydroxide.
6. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is sodium carbonate.
- 25 7. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is potassium carbonate.
8. A composition of any of claims 1 to 3 wherein the sodium or potassium
30 compound is selected from tribasic sodium phosphate and tribasic
potassium phosphate.
9. A composition of claim 8 wherein the sodium or potassium compound
35 is tribasic sodium phosphate.

10. A composition of claim 8 wherein the sodium or potassium compound is tribasic potassium phosphate.
- 5 11. A solid composition for oral administration comprising atorvastatin calcium and either tribasic sodium phosphate or tribasic potassium phosphate.
12. A composition of claim 11 wherein the atorvastatin calcium is
10 amorphous.
13. A composition of claim 11 or 12 comprising tribasic sodium phosphate.
14. A composition of claim 11 or 12 comprising tribasic potassium
15 phosphate.
15. A composition of any of claims 11 to 14 in the form of a tablet.

20

25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00710

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 A61K47/02 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 072073 A (LEK TOVARNA FARMACEVTSKIH ;BAVEC SASA (SI); KERC JANEZ (SI); MATEJ) 19 September 2002 (2002-09-19) page 11, line 4 - line 31 See examples 3-6	1-15
P,X	WO 02 059087 A (LEK TOVARNA FARMACEVTSKIH ;SORSAK GORAZD (SL)) 1 August 2002 (2002-08-01) page 10, line 20 -page 11, line 11	1-15
X	WO 01 93860 A (LEK TOVARNA FARMACEVTSKIH) 13 December 2001 (2001-12-13) page 10, line 7 - line 18 page 11, line 30 -page 12, line 3 page 12, line 15 - line 22 page 13, line 1 -page 14, line 25 --- -/--	1-15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 August 2003

Date of mailing of the international search report

14/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Giménez Miralles, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00710

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 35425 A (LEK TOVARNA FARMACEVTSKIH ;KER & CCARON (SI)) 22 June 2000 (2000-06-22) cited in the application page 7, line 35 -page 8, line 19 page 8, line 33 -page 9, line 6 page 9, line 13 - line 18 -----	1-15
Y	WO 94 16693 A (WARNER LAMBERT CO) 4 August 1994 (1994-08-04) page 15, line 18 - line 33 -----	1-15
Y	US 5 180 589 A (CHIESA PIERINA ET AL) 19 January 1993 (1993-01-19) cited in the application column 1, line 61 -column 2, line 6 -----	1-15
Y	US 5 356 896 A (KABADI MOHAN B ET AL) 18 October 1994 (1994-10-18) cited in the application column 3, line 10 - line 19 -----	1-15
Y	US 2002/035142 A1 (DOROSSIEV IVO ET AL) 21 March 2002 (2002-03-21) cited in the application page 1, paragraph 8 -page 2, paragraph 9 page 2, paragraph 16 -----	1-15

INTERNATIONAL SEARCH REPORT
information on patent family members

International Application No
PCT/CA 03/00710

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02072073	A	19-09-2002	SI 20848 A WO 02072073 A2	31-10-2002 19-09-2002
WO 02059087	A	01-08-2002	SI 20814 A WO 02059087 A1 US 2003109569 A1	31-08-2002 01-08-2002 12-06-2003
WO 0193860	A	13-12-2001	US 6531507 B1 WO 0193860 A1 AU 4943400 A CA 2412326 A1 CZ 20023826 A3 EP 1292293 A1 NO 20025784 A US 2003109584 A1	11-03-2003 13-12-2001 17-12-2001 13-12-2001 16-04-2003 19-03-2003 02-12-2002 12-06-2003
WO 0035425	A	22-06-2000	SI 20109 A AU 6360899 A BG 105559 A CA 2348988 A1 CN 1330538 T CZ 20011727 A3 EP 1148872 A1 HR 20010325 A1 HU 0104258 A2 WO 0035425 A1 JP 2002532409 T PL 347686 A1 SK 8092001 A3 TR 200101235 T2	30-06-2000 03-07-2000 31-12-2001 22-06-2000 09-01-2002 12-09-2001 31-10-2001 30-06-2002 28-03-2002 22-06-2000 02-10-2002 22-04-2002 08-10-2001 22-10-2001
WO 9416693	A	04-08-1994	AT 178794 T CA 2150372 A1 DE 69324504 D1 DE 69324504 T2 DK 680320 T3 EP 0680320 A1 ES 2133158 T3 GR 3030359 T3 JP 3254219 B2 JP 8505640 T MX 9400281 A1 SG 45369 A1 WO 9416693 A1 US 5686104 A US 6126971 A	15-04-1999 04-08-1994 20-05-1999 26-08-1999 25-10-1999 08-11-1995 01-09-1999 30-09-1999 04-02-2002 18-06-1996 29-07-1994 16-10-1998 04-08-1994 11-11-1997 03-10-2000
US 5180589	A	19-01-1993	US 5030447 A AT 79030 T AU 3027689 A CA 1323836 C CN 1036508 A ,B CY 1675 A DE 68902344 D1 DE 68902344 T2 DK 155689 A EP 0336298 A1 HK 40093 A	09-07-1991 15-08-1992 05-10-1989 02-11-1993 25-10-1989 10-10-1993 10-09-1992 07-01-1993 01-10-1989 11-10-1989 30-04-1993

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/CA 03/00710

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5180589	A		IE 62956 B1	08-03-1995
			JP 2006406 A	10-01-1990
			JP 2935220 B2	16-08-1999
			NZ 228076 A	26-04-1991
			SG 107292 G	24-12-1992
			ZA 8901424 A	25-10-1989
US 5356896	A	18-10-1994	AT 401872 B	27-12-1996
			AT 190595 A	15-05-1996
			AT 401870 B	27-12-1996
			AT 244992 A	15-05-1996
			AU 661075 B2	13-07-1995
			AU 3006992 A	17-06-1993
			CA 2085037 A1	13-06-1993
			CH 684309 A5	31-08-1994
			CZ 9203633 A3	15-09-1993
			CY 1994 A	05-09-1997
			DE 4240430 A1	17-06-1993
			DK 547000 T3	26-06-2000
			EP 0547000 A1	16-06-1993
			ES 2142819 T3	01-05-2000
			FI 925615 A	13-06-1993
			FR 2684876 A1	18-06-1993
			GB 2262229 A ,B	16-06-1993
			GR 3032929 T3	31-07-2000
			HK 25597 A	06-03-1997
			HU 221849 B1	28-02-2003
			HU 63328 A2	30-08-1993
			IL 104041 A	27-12-1998
			IT 1256698 B	12-12-1995
			JP 2774037 B2	09-07-1998
			JP 5246844 A	24-09-1993
			KR 253824 B1	01-05-2000
			LU 88201 A1	09-09-1994
			MX 9207152 A1	01-07-1993
			NO 924768 A	14-06-1993
			NZ 245421 A	27-11-1995
			NZ 270729 A	27-11-1995
			PT 547000 T	30-06-2000
			RO 111542 B1	29-11-1996
			RU 2121835 C1	20-11-1998
			SK 363392 A3	09-11-1994
			ZA 9209642 A	13-06-1994
US 2002035142	A1	21-03-2002	AU 5328701 A	23-10-2001
			CA 2406574 A1	18-10-2001
			EP 1274401 A1	15-01-2003
			WO 0176566 A1	18-10-2001